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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 35/413, 45/06, 47/12
// (A61K 35/413, 33/575, 31/405
A61K 31/19, 31/135)

A1

(11) International Publication Number: WO 90/12583

(43) International Publication Date: 1 November 1990 (01.11.90)

(21) International Application Number: PCT/GB90/00605

(22) International Filing Date: 20 April 1990 (20.04.90)

(30) Priority data:
8909022.9 20 April 1989 (20.04.89) GB

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(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.

**Published**
*With international search report.*

(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

Pharmaceutically active agents are formulated with a bile salt and at least one additional component of bile. The bile salt and additional component may be provided as a naturally occurring bile mix, such as a methanolic extract of animal (for example, ox) bile. A lymphatic absorption promoter such as oleic acid or glycerol mono-oleate may also be present. Pharmaceuticals formulated in this way can benefit from enhanced bioavailability, particularly as hepatic first-pass metabolism is reduced. NSAIDs and cardiovascular agents are particularly suitable for formulation by means of the invention.

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# PHARMACEUTICAL COMPOSITIONS

This invention relates to pharmaceutical compositions which: promote the solubility of drugs which are only poorly soluble in water; protect drugs when orally administered, from the hostile acidic and enzymatic environment of the stomach; protect the gastrointestinal mucosa from the harmful effects of such drugs as non-steroidal anti-inflammatory drugs (NSAIDs); increase the bioavailability of drugs, particularly those normally subject to significant hepatic first-pass metabolism; and/or contain generally inexpensive excipients. The invention also relates to a method of formulating a pharmaceutically active agent into a pharmaceutical composition and to methods of administering drugs, as well as to the use of drugs and certain other ingredients in the preparation of pharmaceutically useful compositions.

It is in general known to formulate surfactants with pharmaceutical agents for the purpose of solubilising them as in, for example, EP-A-0179583. EP-A-0274870 teaches that NSAIDs, which are in general poorly water soluble, can be administered, as well as solubilised, as micelles and that this has advantages of (a) potentially protecting the drug from the acidic and enzymatic environment of the stomach and (b) protecting the gastrointestinal mucosa from adverse effects of the drug (such as gastrointestinal bleeding, which is induced by NSAIDs including aspirin, indomethacin and piroxicam).

Bile acids (or bile salts - the terms are used interchangeably in this specification) are naturally occurring surfactants. They are a group of compounds with a common "backbone" structure based on cholanic acid found in all mammals and higher vertebrates. The detergent properties of bile acids are largely determined by the number and orientation of hydroxyl groups substituted onto a steroidal nucleus. Bile acids may be mono-, di- or tri-hydroxylated; they always contain a 3-alpha hydroxyl group, whereas the other hydroxyl groups, most commonly found at $C_6$, $C_7$ or $C_{12}$, may be positioned above (beta) or below (alpha) the plane of the molecule. Many permutations of hydroxyl configuration are possible, but certain configurations are very much more common in nature than others. In most animal species there is a recognised pattern to the usual composition of the bile acids found in the bile acid pool of individual animals.

Bile acids are synthesised <u>in vivo</u> from cholesterol in the liver by hydroxylation and other modifications. Virtually all bile acids found in the bile of mammals and higher vertebrates are amidated at the $C_{24}$ position with either taurine or glycine. The extent to which various bile acids are amidated with either glycine or taurine shows considerable variation between species and depends on the availability of taurine as a substrate for the conjugating enzyme.

Bile acids have various physiological functions. Conjugated bile acids are secreted rapidly into the bile by the liver, where they provide a means of generating water flow by osmosis. It is in the

duodenum that bile acids perform their major role as surfactants: they function to enhance the digestion and absorption of dietary lipids and lipid soluble vitamins. Bile acids also increase the action of pancreatic lipases.

Miyazaki et al (Chem. Pharm. Bull. 27 (10) 2468-72 (1979)) have suggested that sodium desoxycholate and sodium cholate enhance the dissolution of indomethacin and phenylbutazone in pH 7.3 buffer at 37°C.

While in principle the addition of individual bile salts to, for example, NSAIDs might take the place of the particular surfactants disclosed in EP-A-0274870, in practice, there are a number of problems with this approach:

(a) Individual bile salts are generally too expensive to be commercially useful;

(b) Individual bile salts have low (and variable) solubilising powers on their own; and

(c) Certain bile salts promote absorption of some drugs (Kimura et al (Chem. Pharm. Bull. 20 (8) 1656-62 (1972))) whereas some some inhibit absorption (Yamaguchi et al (Chem. Pharm. Bull. 34 (8) 3362-69 (1986))).

It has now been discovered that additional components from bile can confer advantageous properties on pharmaceutical compositions containing a

phamaceutically active agent and a bile salt. Solubilisation properties and/or drug delivery characteristics may be improved.

According to a first aspect of the present invention, there is provided a pharmaceutical composition comprising a pharmaceutically active agent, a bile salt and at least one additional component (other than water) of bile.

The additional component, or one additional component, may be a different bile salt. Alternatively or additionally, the additional component, or one additional component, may be a component of bile which is not a bile salt and which may be a biliary lipid such as a phospholipid. Biliary lipids are believed to enhance micellisation and promote the lymphatic absorbtion of lipids and lipid-soluble vitamins. It is preferred to have more than one bile salt and one or more other biliary components (such as biliary lipids) present.

Native bile from most mammalian species contains large quantities of the phospholipid phosphatidylcholine. The phosphatidylcholine found in bile is of a highly specific nature, quite different from that making up the structural elements of the membranes of hepatocytes and the cells surrounding the biliary tree.

The distinctive nature of biliary phosphatidylcholine is determined by its constituent fatty acids: palmitic acid (C:16) or palmitoleic acid (C16:1) being esterified to the sn1-position, and either oleic acid

(C18:1), linoleic acid (C18:2) or linolenic acid (C18:3) esterified to the sn2-position of the glycerol backbone of the phospholipid. The exact distribution of these fatty acid types in biliary phosphatidylcholine does, however, vary considerably between species.

The importance of these subclasses of phosphatidylcholines, which are derived from a metabolically compartmentalized synthetic pathway destined to produce phosphatidycholine for secretion from hepatocytes, is their ability to form expanded mixed micelles when combined with bile acids. Thus, by acting as swelling amphiphiles they greatly enhance the ability of bile acids to act as surfactants. For example, bile acids have little tendency to solublize non-polar lipids such as cholesterol in the absence of phosphatidylcholine. This is important in vivo, where biliary phosphatidylcholine is believed to aid the incorporation of biliary cholesterol into bile acid mixed micelles. Failure of this system to function correctly probably leads to the formation of cholesterol gallstones in man. In addition to their function in bile, biliary phosphatidylcholines are believed to enhance the micellization of lipids in the duodenum. This function may be carried out by intact phosphatidylcholine or equally as well by, and in conjunction with, its natural degradation products such as lysophosphatidylcholine and free fatty acids.

The inclusion of materials of this type in compositions in accordance with te present invention appear greatly to enhance solubilisation properties and/or drug

delivery characteristics observed when compared to those in the studies using formulations containing purified bile acids. The quantities of pure bile acids required to produce pharmacologically useful effects (see Kimura et al, Chem. Pharm. Bull, 20 (10), 2468-72 (1979); Yamaguchi et al, Chem. Pharm. Bull, 34, (8), 3362-69 (1986)) as active excipients in a drug delivery system would preclude their incorporation in a conventional dose form. Furthermore, their reliance on very high concentrations of pure bile acids would rule out their use on the basis of likely toxic side effects when used repeatedly over long periods. In contrast, when using the excipients used in the present invention, the quantities administered remain considerably below the levels of bile acids lost daily from the host's bile acid pool. It is therefore unlikely that the use of relatively small amounts of bile acid of natural sources would be sufficient to overload the systems used to handle the host's own endogenous bile acids.

The bile salt and additional biliary component may conveniently be provided by a naturally occurring mix of bile components including bile salts such as animal bile itself or an extract of bile. The naturally occurring mix of bile components may be that naturally occurring in any animal, preferably a domestic livestock animal, as the bile components would be available from the abattoir. Suitable animal sources of bile components include oxen, pigs, sheep and other animals. One suitable naturally occurring mixture of bile components may be produced simply by evaporating natural bile (for example ox bile) to dryness. Ox bile

extract, prepared in this way, is a dark yellow-greenish powder containing a variety of bile acids of which taurocholate is the most prevalent. Bile acids themselves typically make up 50 to 60% of the dry weight of the powder, bile pigments 5 to 10%, and sulphated ash 10 to 20%; HPLC analysis indicates that for ox bile total bile aids account for 69% of dry weight, of which 17.5% is taurocholate, 14.1 % cholic acid, 7.4% taurochenodeoxycholate, 6.1% taurodeoxycholate, 1.7% taurolithocholate and 1% minor bile acids. In addition, there may also be small amounts of cholesterol and phospholipid, as discussed above, together with lipid and protein degradation products formed in the manufacturing process.

A crude (but in some circumstances suitable) naturally occurring mixture of bile components may be prepared simply by drying bile from the abattoir. To achieve this, the bile may be subjected to four processing stages: evaporating, drying, milling and sieving. For example, crude bile may be first reduced to a concentrate. This may be done in one or more stages; in one embodiment of the invention, the crude bile is first reduced to a 50 to 60% concentrate, which is a paste which is then transferred to a further evaporation system to reduce it to a 70 to 80% concentrate. The material may be finally dried to substantially complete dryness, for example in a vacuum oven over a period of about 4 days. The resulting material has the consistency of brittle toffee and is hygroscopic in nature. This may be milled, for example

into a powder. Milling can be carried out in a ball mill, for example for 2 hours, after which it may be sieved and packaged into appropriate containers.

It is generally preferred to use a somewhat more refined bile salt mixture than is obtained as the direct result of the above process. A refined extract may be prepared by extraction with a simple organic solvent such as an alcohol (for example $C_1$ to $C_4$ alcohols) or a ketone (for example, acetone). Methanol is a preferred extraction solvent. An advantage of refining the crude ox bile extract is that this step removes certain mineral salts.

The pharmaceutically active agent and the mixture of bile components are preferably intimately admixed together. Such an intimate admixture may be produced by grinding a solid preparation of the pharmaceutically active agent with solid bile salt mixture, crude or refined, as discussed above, to a very fine particle size, for example less than 100 microns or even less than 10 microns. It is however preferred to produce the intimate admixture by dissolving the pharmaceutically active agent and the bile salt mixture in a common solvent and evaporating the solvent off. It is particularly convenient if the same solvent is used for this purpose as is used to refine the bile components from a crude extract. As discussed above, alcoholic solvents such as methanol are particularly preferred. Other formulatory excipients, such as enteric coating materials, may be found to be soluble in the solvent of choice and, conversely, the solvent will often be chosen with the solubility of other

excipients in mind. The solvent can be evaporated off in a rotary evaporator, possibly under reduced pressure conditions, for small scale preparations or in a drum dryer on a larger scale.

Many of the advantages of the invention will be realised with orally administerable compositions, and such compositions are therefore preferred. Often, the compositions will be substantially non-aqueous, by which is meant containing less than 30, 20, 10 or even 5% water by weight.

It is preferred that pharmaceutical compositions in accordance with the invention be produced in the form of pellets, as these can provide a suitable basis for further coating. Examples of functional types of coating include: enteric coating to provide protection of the contents from ionic disturbances in high acid gastric media, as well as providing additional protection of the stomach from the drug; sustained release or controlled release coatings; and/or film coating for rapid release preparations. Film coatings for rapid release are preferred, as bile salts are hygroscopic and uncoated pellets may be difficult to handle if left standing, as they may have a tendency to stick together to an unacceptable degree.

Pharmaceutical compositions in accordance with the invention which are pellets may be prepared by coating a solution (for example the preferred methanolic solution) of the pharmaceutical active ingredient and the bile salt mixture onto a suitable carrier such as granulated sugar crystals. The crystals may be from

100 to 1000 microns in diameter, for example from 500 to 850 microns. The coating can be conveniently achieved in a fluidised bed spray-coating machine, for example using the Wurster configuration, or in a semi-fluidised bed, for example using the bottom rotating plate configuration, as in the ROTOR-GRANULATOR device manufactured by Glatt or the ROTO-PROCESSOR device manufactured by Aeromatic. (The words ROTOR-GRANULATOR and ROTO-PROCESSOR are trade marks. Top spraying is another suitable technique.

Other excipients may be present. For example, plasticisers and/or binding agents may be used when coating seed crystals or other matrix materials. Suitable plasticisers include polyvinyl pyrrolidone (povidone), hydroxypropyl methyl cellulose (HPMC), propylene glycol, polyethylene glycol or hydroxypropyl cellulose. Some of these materials can function as additional solubilising agents, and the presence of these or other solubilising agents is also within the scope of the invention. Lecithin is a suitable lipid solubilising agent, as are its naturally occurring breakdown products, lysolecithin and free fatty acids.

A particularly preferred excipient is a lymphatic absorbtion promoter. Examples of such materials, which can be absorbed directly by enterocytes which surround the gastrointestinal tract, will be known to those skilled in the art. For the purposes of the present invention, long chain (eg at least $C_{12}$ and preferably $C_{12}$-$C_{24}$) fatty acids and their mono-esters, such as with glycerol, are preferred. The acids and their esterified derivatives may be saturated or (mono- or poly-) unsaturated. Lymphatic absorbtion promoters which have been found to perform well in the compositions of the present invention include oleic acid and glycerol mono-oleate.

The amount of lymphatic absorbtion promoter present will depend on its nature and the nature of the pharmaceutically active agent. In general, the lymphatic absorbtion promoter may be present in an amount of from 1 to 100% (w/w or v/w) based on the amount of active agent, preferably from 5 to 50% and typically from 10 to 35%.

Pharmaceutical compositions in accordance with the invention may be found to be relatively soluble in intestinal fluid, compared to the solubility in an acidic aqueous environment, such as is found in the stomach. This may be at least partly due to the formation of a dark gummy mass which is a complex formed by the components of the bile salt mixture in acidic conditions. Although the dark gummy mass does appear to dissolve in intestinal fluid, it takes longer

to do so than if it had not been exposed to acid, and for this reason it is generally preferred that the mixture of the pharmaceutically active agent and the bile component mixture be protected from the acidic stomach environment. This can be achieved by enteric coating, as discussed above.

The mixture may be encapsulated in capsules such as hard gelatin capsules, but any convenient capsules can be used.

The present invention can be used to formulate practically any pharmaceutically active agent conveniently and relatively inexpensively. The invention finds particular application in formulating those pharmaceutically active agents which need protection from the acidic environment of the stomach and/or those from which the gastrointestinal mucosa needs protection. Non-steroidal anti-inflammatory drugs (NSAIDs) are examples of such pharmaceutically active agents.

NSAIDs (or aspirin-like drugs - the two terms are used interchangeably in this specification) can be categorised conveniently into six structural groups. First, there are the salicylic acids and esters including aspirin, benorylate, aloxiprin, salsalate and choline magnesium trisalicylate. Secondly, there are the propionic acid derivatives, including ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, benoxaprofen and suprofen. Thirdly, there is the class of oxicams, including piroxicam. Fourthly, acetic acid derivatives can be split into two

subclasses. Phenylacetic acids include diclofenac and fenclofenac; carbo- and heterocyclic acetic acids include indoles such as indomethacin and sulindac and pyrroles such as tolmetin. Fifthly, there are the pyrazolones which include oxyphenbutazone, phenylbutazone, feprazone and azapropazone. Sixthly, the fenamic acid derivatives include flufenamic acid and mefenamic acid.

Of the above NSAIDs, there are some which can be formulated particularly satisfactorily by means of the present invention, particularly when using methanol as a solvent for both the NSAID and the bile salt mixture. These are: indomethacin, diclofenac, sulindac, naproxen, piroxicam and mefanamic acid.

The present invention is not only useful for formulating NSAIDs. In particular, it is useful for formulating pharmaceutically active agents which are subject to significant hepatic first-pass clearance, as will now be discussed.

Administration of standard pharmaceutical preparations via the oral route conventionally results in the majority of the absorbed drug entering the hepatic portal venous blood supply. Subsequently, this venous system, draining most of the gastrointestinal tract, passes directly through the liver without mixing with the systemic blood supply. The consequence of this is that many therapeutic agents conventionally undergo an extensive first-pass clearance and metabolism, by means of the liver's detoxification system, with the net result that the material reaching the systemic blood

supply is very much reduced. In order to obtain therapeutically effective concentrations in the systemic circulation, relatively large doses have had to be administered. A further problem is that the nature and extent of the hepatic first-pass effect displays considerable inter- and intra-subject variation.

The implications of the first-pass effect are therefore that wide variations in systemic blood levels of a compound can be obtained from the same orally administered dose leading to the possibility of increased incidence of side-effects or toxic reaction if the dose is too high, or even to a failure to control symptoms at all if a very extensive first-pass effect is present.

By means of the present invention, it may be possible to avoid or reduce a hepatic first-pass clearance, as there is evidence to suggest that pharmaceutical compositions in accordance with the invention cause redirection from the portal blood to the lymphatic route of absorption from the gastrointestinal tract. That the lymphatic system avoids the liver is a function of its anatomy in that the major lymphatic vessels, into which the gastrointestinal lymph system drains, come together in the thoracic duct, which then empties directly into the systemic circulation.

In a particularly preferred embodiment of the invention, therefore, the pharmaceutically active agent is one which is normally subject to significant hepatic

first-pass metabolism. Such pharmaceutically active agents include, but are not restricted to, a number of cardiovascular agents.

Cardiovascular agents which may in particular be formulated by means of the present invention include propranolol, metoprolol, verapamil, nifedipine and diltiazem, either in the form of the free compound or, where appropriate, as a salt. Atenolol and nadolol are not subjected to first-pass metabolism but may nevertheless be formulated with advantage in accordance with the invention, for example in order to increase their generally poor absorbtion.

Other pharmaceutically active agents which are subject to a hepatic first-pass clearance to a significant degree and/or which are poorly absorbed, or indeed any other pharmaceutically active agent, may be formulated by means of the present invention.

According to a second aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition, the process comprising admixing a pharmaceutically active agent, a bile salt and at least one additional component (other than water) of bile. The bile salt and the additional component(s) can be a premixture, such as by being part of a naturally occurring mixture of bile components, before the pharmaceutically active agent is mixed.

It will be appreciated that the invention can be used in a method of chemotherapeutic treatment of a human or animal patient, the method comprising the

administration of a composition in accordance with the first aspect of the invention. The invention also encompasses the use of a pharmaceutically active agent, a bile salt and at least one additional component (other than water) of bile (which may be provided by a naturally occurring mixture of bile components) in the preparation of a pharmaceutical composition.

The invention will now be illustrated by means of the following preparation and examples.

Preparation 1 - Crude Ox Bile Extract

Crude bile, collected from the abattoir, is pumped into a stainless steel tank and heated by steam coils and reduced to a 50 to 60% concentrate. The resulting paste is transferred to an open steam jacketed evaporating pan system and reduced further to a 70 to 80% concentrate. Final drying of the material took place in a vacuum oven over a period of about 4 days. The resulting material had the consistency of brittle toffee and was hygroscopic in nature. The solid material was milled into a powder in a ball mill for 2 hours and then sieved and packaged into fibre-board drums lined with polythene bags.

Preparation 2 - Crude Pig Bile Extract

Pig bile powder, which is light brown in colour, was prepared in a similar fashion to ox bile powder, as described in Preparation 1. Examples 28 to 46 illustrate the possible use of an alternative animal source of biliary material for use in pharmaceutical

preparations. Pig bile has a different bile acid composition to ox bile since it contains mainly hyocholic acid instead of cholic acid.

Example 1

4.0g crude ox bile extract, as prepared in Preparation 1, was dissolved in 17.5g methanol. The solution was heated with stirring and boiled for 10 minutes. After allowing to cool, it was filtered through WHATMAN No. 4 filter paper. The methanol was made up to its original volume and 1.0g indomethacin was added. After dissolving the indomethacin with stirring, the solution was evaporated in an EVAPOTEC Rotory Film Evaporater, the water bath temperature being approximately 50°C and a strong vacuum being maintained. The product crystals were recovered and found to dissolve very rapidly and completely in pH 6.8 phosphate buffer. (The words WHATMAN and EVAPOTEC are trade marks.)

Example 2

4.0g of crude ox bile extract, as prepared in Preparation 1, was dissolved in 15g methanol and the solution was boiled for 30 minutes. After allowing to stand, the solution was filtered and the filtrate was made up to its original volume with methanol. 2.0g indomethacin, 0.5g povidone and 0.5g hydroxypropyl methylcellulose were dissolved in the resulting solution before evaporating to dryness as described in Example 1.

Example 3

4.0g of crude ox bile extract, as prepared in Preparation 1, was dissolved in 25g methanol and the solution was boiled for 30 minutes. After allowing to stand, the solution was filtered and the filtrate was made up to 100ml with methanol in order to achieve dissolution of the 4.0g indomethacin and 0.8g povidone which were added to it. The solution was evaporated to dryness as described in Example 1. The crystalline product dissolved easily in pH 6.8 buffer solution.

Example 4

The procedure of Example 3 was followed, but using the following quantities of ingredients:

| | |
|---|---|
| Crude ox bile extract powder | 3.0g |
| Methanol | 25g |
| Indomethacin | 1.0g |

A crystalline product was obtained.

Example 5

2.0g of crude ox bile extract, as prepared in Example 1, was dissolved in 10g methanol and the resulting solution was boiled for 15 minutes before cooling and filtering through a WHATMAN No. 4 filter. 4.0g of naproxen acid was dissolved in the filtrate which was made up to its original volume with methanol. The solution was evaporated to dryness as described in

Example 1. A dense crystalline product was obtained which was slowly soluble in pH 6.8 phosphate buffer solution.

Example 6

4.0g of crude ox bile extract, as prepared in Example 1, was dissolved in 25g methanol and the resulting solution was boiled for 30 minutes before cooling and filtering through a WHATMAN No. 4 filter. 5.0g of naproxen acid and 0.5g povidone were dissolved in the filtrate which was made up to its original volume with methanol. The solution was evaporated to dryness as described in Example 1. A dense crystalline product was obtained which was slowly soluble in pH 6.8 phosphate buffer solution.

Example 7

4.0g of crude ox bile extract, as prepared in Example 1, was dissolved in 25g methanol and the solution was boiled for 30 minutes following cooling and filtering through a WHATMAN No. 4 filter. 4.0g diclofenac acid and 0.8g povidone were dissolved in the filtrate which was taken up to 70ml with methanol. The solution was evaporated to dryness as described in Example 1 and fine soft crystals were produced which dissolved rapidly and completely in pH 6.8 buffer solution.

Example 8

4.0g of crude ox bile extract, as prepared in Example 1, was dissolved in 25g methanol and the solution was boiled for 30 minutes following cooling and filtering through a WHATMAN No. 4 filter. 4.0g sulindac and 0.5g povidone were dissolved in the filtrate which was taken up to 100ml with methanol. The solution was evaporated to dryness as described in Example 1 and fine soft crystals were produced which dissolved rapidly and completely in pH 6.8 buffer solution.

Example 9

462g of crude ox bile extract, as prepared in Preparation 1, was dissolved in 1000g methanol. The solution was warmed to 30°C and then allowed to stand for one hour before being pressure filtered using WHATMAN GF/D filters. 154g indomethacin and 62g povidone were dissolved in the filtrate which was taken to a total volume of 3.4 litres with methanol. A UNI-GLATT fluidized bed, fitted with a WURSTER insert, was used to coat 500g of granulated sugar sieved to 500-850 microns. The product temperature was maintained at approximately 40°C and the coating rate was approximately 450ml/hour. The resulting pellets were sieved between 500 and 1400 microns to remove fines and oversize, and they were then sprayed with a film coat consisting of 25g of hydroxypropyl methylcellulose dissolved in 300ml methanol. The resulting pellets were essentially spherical with a smooth glossy surface. They had a bulk density of 0.82g/ml and a potency of 126mg indomethacin per gram.

They readily dissolved in pH 6.8 buffer solution. These pellets were filled into size "1" hard gelatin capsules with a mean fill weight of 398mg, giving a potency of 50mg indomethacin per capsule.

The same solution can be used to make pellets for filling into Size "2" hard gelatin capsules, with a potency of 25mg per capsule. The quantity of sucrose core material is adjusted to give the require potency, according to the following proportions:

| | |
|---|---|
| Refined ox bile extract* | 75 |
| Indomethacin | 25 |
| Povidone | 10 |
| Hydroxypropyl methylcellulose | 4 |
| Sucrose (500-800 micron) | 181 |
| | 295mg |

* Ox bile extract after methanolic extraction

Example 10A

75mg indomethacin capsules were prepared, suitable for sustained release, using the following proportions of materials:

| | |
|---|---|
| Crude ox bile extract (Preparation 1) | 150 |
| Indomethacin | 75 |
| Povidone | 20 |
| Sucrose (500-800 micron) | 115 |
| | 360mg |

This formulation allows for a 40mg sustained release coat.

Example 10B

A lower ratio of crude ox bile extract/indomethacin was tried, as follows:

300g of crude ox bile extract was dissolved in 1000g methanol. The solution was boiled for 30 minutes, left to stand overnight, and then pressure filtered. 300g indomethacin and 60g povidone were dissolved in the filtrate which had to be made up to 7.2 litres with methanol so as to achieve full dissolution of the indomethacin. The resulting solution was sprayed onto 340g sucrose (500-850 micron) in a UNI-GLATT fluidized bed as described in Example 9. The resulting pellets dissolved satisfactorily in pH 6.8 phosphate buffer solution. Note that the solubility of indomethacin in methanol decreases as the ratio of refined ox bile extract/indomethacin decreases. The preferred proportions given in Example 10A allow a higher solubility of indomethacin in the spraying solution, and hence a reduced volume of coating solution to be sprayed.

Example 11

Pellets of naproxen were prepared according to the methods described for Example 9, using the following proportions of materials, but excluding the final film coat:

| | |
|---|---|
| Crude ox bile extract | 100g |
| Methanol | 600g |

The solution was boiled for 30 minutes, allowed to stand overnight and pressure filtered.

| | |
|---|---|
| Naproxen acid | 200g and |
| Povidone | 15g |

were then dissolved. The total solution volume was made up to 2.6 litre with methanol and coated on to:

| | |
|---|---|
| Sucrose (500-850 micron) | 330g |

This provides a partial coating. In order to achieve a potency of 250mg per capsule, it would be necessary to apply more coating solution to the above pellets, and if using the UNI-GLATT fluidised bed to divide the batch into two sub-batches, and then coat each sub-batch until the required potency is achieved.

Example 12

Pellets of diclofenac were prepared using the following proportions of materials and the methods of Example 9, but without the final film coat:

| | |
|---|---|
| Crude ox bile extract | 200g |
| Methanol | 1000g |

Boil 30 minutes, stand overnight, pressure filter.

| | |
|---|---|
| Diclofenac acid | 200g |
| Povidone | 40g |

Dissolve in the filtrate with total volume being made up to 2.0 litres with methanol. coat on to:

| | |
|---|---|
| Sucrose (500-850 micron) | 240g |

The potency of the pellets is such that, after adding a film coating or controlled release coating, 100mg of diclofenac will be filled into a Size "1" gelatin capsule.

Example 13

Pellets of sulindac were prepared according to the methods described for Example 9, using the following proportions of materials, but excluding the final film coat:

| | |
|---|---|
| Crude ox bile extract | 200g |
| Methanol | 1000g |

Boil 30 minutes, stand overnight, pressure filter.

| | |
|---|---|
| Sulindac | 200g |
| Povidone | 20g |

Dissolve in the filtrate with the total volume being taken up to 2.0 litre with methanol.

Coat on to:

| | |
|---|---|
| Sucrose (500-850 micron) | 340g |

The resulting pellets, after having a final film coating, could be filled in to Size "1" hard gelatin capsules to give a potency per capsule of 100mg sulindac. If 200mg capsules are required, the above coating represents one-quarter of the coating solution requirements. Splitting of the batch into two sub-batches would be necessary when using the UNI-GLATT fluidised bed after half the total coating solution has been applied.

Example 14

Pellets of piroxicam were prepared according to the methods described for Example 9, using the following proportions of materials:

| | |
|---|---|
| Crude ox bile extract | 300g |
| Methanol | 1000g |

Boil 30 minutes, stand overnight, pressure filter.

| | |
|---|---|
| Piroxicam | 60g |
| Povidone | 45g |

Dissolve in the filtrate with the total volume being taken up to 2.4 litre with methanol.

Coat on to:

| | |
|---|---|
| Sucrose (500-850 micron) | 435g |

Apply final film coat of:

| | |
|---|---|
| Hydroxypropyl methylcellulose | 45g in |
| Methanol | 500ml |

The resulting pellets had a bulk density of 0.86 g/ml and a potency such that 20mg piroxicam could be achieved when the pellets were filled into Size "2" capsules. The pellets readily dissolve in pH 6.8 phosphate buffer solution.

Example 15

5g oxide ox bile extract powder, as prepared in Preparation 1, was added to 15ml of methanol and boiled under reflux for 15 minutes on a heated magnetic stirring plate. The cooled methanolic solution was left overnight before being filtrated through a WHATMAN No. 4 filter paper. The weight of methanol lost during preparation was replaced and 1g of propranolol hydrochloride dissolved. A fine greenish-yellow crystalline product was easily recovered under rotary evaporation containing an ox bile powder:propranolol hydrochloride ratio of 5:1.

Example 16

The procedure described in Example 15 was followed, using the following ingredients:

| | |
|---|---|
| Crude ox bile extract powder | 5.0g |
| Methanol | 15.0g |
| Propranolol base | 1.0g |

A greenish-yellow crystalline product was formed.

Example 17

The procedure described in Example 15 was used, with the following ingredients:

| | |
|---|---|
| Crude ox bile extract powder | 5.0g |
| Methanol | 15.0g |
| Atenolol | 1.0g |

A greenish-yellow crystalline product was formed.

Example 18

The procedure outlined in Example 15 was used, with the following ingredients:

| | |
|---|---|
| Crude ox bile extract powder | 5.0g |
| Methanol | 15.0g |
| Metoprolol | 1.0g |

A crystalline product was obtained.

Example 19

The procedure outlined in Example 15 was used, with the following ingredients:

| | |
|---|---|
| Crude ox bile extract powder | 5.0g |
| Methanol | 15.0g |
| Diltiazem | 1.0g |

A crystalline product was obtained.

Example 20

The procedure outlined in Example 15 was used, with the following ingredients:

| | |
|---|---|
| Crude ox bile extract powder | 5.0g |
| Methanol | 15.0g |
| Verapamil | 1.0g |

A crystalline product was obtained.

Example 21

The procedure outlined in Example 15 was used, with the following ingredients:

| | |
|---|---|
| Crude ox bile extract powder | 5.0g |
| Methanol | 15.0g |
| Nifedipine | 1.0g |

A bright yellow crystalline product was formed.

Example 22

2g of crude ox bile extract powder, as prepared in Preparation 1, was added to 15ml of methanol and boiled under reflux for 15 minutes on a heated magnetic

stirring plate. The cooled methanolic solution was allowed to stand overnight and then filtered through a WHATMAN No. 4 filter paper. The weight of methanol was restored to that present at the beginning of the example and 1g of propranolol hydrochloride was dissolved. A greenish-yellow crystalline product was obtained upon removal of the methanol by rotary evaporation under reduced pressure. The final ratio of ox bile extract:propranolol was 2:1.

Example 23

The same procedure described in Example 22 was carried out, using the ingredients listed below:

| | |
|---|---|
| Crude ox bile extract powder | 2.0g |
| Methanol | 15.0g |
| Propranolol base | 1.0g |

A crystalline product was recovered.

Example 24

The same procedure described in Example 22 was carried out, using the ingredients listed below:

| | |
|---|---|
| Crude ox bile extract powder | 2.0g |
| Methanol | 15.0g |
| Atenolol | 1.0g |

Atenolol was a little slow to dissolve in the methanolic solution, but still formed a crystalline product.

Example 25

The same procedure described in Example 22 was carried out, using the ingredients listed below:

| | |
|---|---|
| Crude ox bile extract powder | 2.0g |
| Methanol | 15.0g |
| Diltiazem | 1.0g |

A crystalline product was formed.

Example 26

The same procedure described in Example 22 was carried out, using the ingredients listed below:

| | |
|---|---|
| Crude ox bile extract powder | 2.0g |
| Methanol | 15.0g |
| Verapamil | 1.0g |

A crystalline product was formed.

Example 27

The same procedure described in Example 22 was carried out, using the ingredients listed below:

| | |
|---|---|
| Crude ox bile extract powder | 2.0g |
| Methanol | 15.0g |
| Nifedipine | 1.0g |

A yellow crystalline product was formed.

Example 28

5.0g of pig bile extract powder, as prepared in Preparation 2, was dissolved in 15ml of methanol and boiled under reflux for 15 minutes on a heated magnetic stirring plate. The cooled methanolic solution was allowed to stand overnight and then filtered through a WHATMAN No. 4 filter paper. The weight of methanol was restored to 15.0g. 1g of naproxen was added and mixed until dissolved. Upon removal of the methanol by rotary evaporation, a light brown crystalline product was formed.

Example 29

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract powder | 5.0g |
| Methanol | 15.0g |
| Ketoprofen | 1.0g |

A yellow crystalline product was formed.

Example 30

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Diclofenac | 1.0g |

A yellow crystalline product was formed.

Example 31

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Sulindac | 1.0g |

A bright yellow crystalline product was formed.

Example 32

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract powder | 5.0g |
| Methanol | 15.0g |
| Indomethacin | 1.0g |

A yellow crystalline product was formed.

Example 33

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Flufeamic acid | 1.0g |

A yellow crystalline material was formed.

Example 34

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Ibuprofen | 1.0g |

A yellow crystalline product was formed.

Example 35

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Atenolol | 1.0g |

A yellow crystalline product was formed.

Example 36

The same procedure describe din Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Diltiazem HCl | 1.0g |

A yellow crystalline product was formed.

Example 37

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Diltiazem base | 1.0g |

A yellow crystalline product was formed.

Example 38

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Propranolol HCl | 1.0g |

A yellow crystalline product was formed.

Example 39

The same procedure described in Example 28 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 5.0g |
| Methanol | 15.0g |
| Propranolol base | 1.0g |

A yellow crystalline product was formed.

Example 40

2.0g of pig bile extract was added to 15ml of methanol and boiled under reflux for 15 minutes on a heated magnetic stirring plate. The cooled methanolic solution was allowed to stand overnight and filtered through a WHATMAN No. 4 filter paper. The weight of methanol was restored to that present at the beginning of the example and 1g of naproxen was dissolved. A light-brown crystalline product was recovered upon removal of the methanol by rotary evaporation under reduced pressure. The final ratio of pig bile extract:naproxen was 2:1.

Example 41

The same procedure described in Example 40 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 2.0g |
| Methanol | 15.0g |
| Ketoprofen | 1.0g |

A yellow crystalline product was formed.

Example 42

The same procedure described in Example 40 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 2.0g |
| Methanol | 15.0g |
| Diclofenac | 1.0g |

A light-yellow crystalline product was recovered.

Example 43

The same procedure described in Example 40 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 2.0g |
| Methanol | 15.0g |
| Sulindac | 1.0g |

A light-yellow crystalline product was recovered.

Example 44

The same procedure described in Example 40 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 2.0g |
| Methanol | 15.0g |
| Indomethacin | 1.0g |

A yellow crystalline product was removed.

Example 45

The same procedure described in Example 40 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 2.0g |
| Methanol | 15.0g |
| Flufenamic acid | 1.0g |

A yellow crystalline product was recovered.

Example 46

The same procedure described in Example 40 was carried out using the ingredients listed below:

| | |
|---|---|
| Pig bile extract | 2.0g |
| Methanol | 15.0g |
| Diltiazem HCl | 1.0g |

A yellow crystalline product was recovered.

Example 47 - Dissolution Study using Ox Bile Extract Powder

The aim of the simple dissolution study was to obtain a basic idea of how each formulation would behave under the varying pH conditions experienced in the stomach and duodenum. Three separate solutions were used, U.S.P. intestinal fluid simulated pH 7.4 (no enzymes), U.S.P. intestinal fluid simulated pH 1.27 (no enzymes), and distilled water. Tests were carried out in small glass bottles, containing either 120mg or 60mg of each formulation depending upon whether the 5:1 or 2:1 excipient to active ratio material was used. Separate dissolution studies were carried out at 25°C and 37°C using 10ml of each test solution.

a) Solubility at pH 7.4

The following remained in a clear stable solution in pH 7.4 buffer at both 25°C and 37°C.

| | | |
|---|---|---|
| i) | Propranolol hydrochloride | (5:1) |
| ii) | Propranolol base | (5:1) |
| iii) | Atenolol | (5:1) |
| iv) | Diltiazem | (5:1) |
| v) | Metoprolol | (5:1) |
| vi) | Atenolol | (2:1 and 5:1) |
| vii) | Diltiazem | (2:1 and 5:1) |
| viii) | Metoprolol | (2:1 and 5:1) |

Verapamil (5:1) formed an emulsion but remained in solution, while nifedipine (5:1) remained in solution for a few minutes before forming a precipitate and may therefore require higher ratios of ox bile extract.

b) Solubility in Water

The following dissolved in water at 25°C and 37°C, to form clear stable solutions:

| | | |
|---|---|---|
| i) | Atenolol | (5:1) |
| ii) | Diltiazem | (5:1) |
| iii) | Metoprolol | (5:1) |
| iv) | Atenolol | (2:1) |
| v) | Metoprolol | (2:1) |

c) Solubility at pH 1.27

None of the formulations formed a clear stable solution at pH 1.27. However, the following produced a clear solution over a gummy solid:

| | | |
|---|---|---|
| i) | Propranolol hydrochloride | (5:1) |
| ii) | Verapamil | (2:1) |
| iii) | Metoprolol | (5:1) |

The remaining formulations formed a cloudy precipitate at pH 1.27; nevertheless, the following also contained a gummy solid:

| | | |
|---|---|---|
| i) | Atenolol | (5:1) |
| ii) | Diltiazem | (5:1) |
| iii) | Propranolol base | (5:1) |
| iv) | Diltiazem | (2:1) |
| v) | Metoprolol | (2:1) |

Example 48

Dissolution Studies using Pig Bile Extract Powder

A similar dissolution protocol was used to that described in Example 28 except that formulations contained pig bile extract powder.

a) Solubility at pH 7.4

The following remained in a clear stable solution in pH 7.4 at both 25°C and 37°C.

NSAIDs

| | | |
|---|---|---|
| i) | Naproxen | (2:1) and (5:1) |
| ii) | Ketoprofen | (2:1) and (5:1) |
| iii) | Diclofenac | (2:1) and (5:1) |
| iv) | Sulindac | (2:1) and (5:1) |
| v) | Indomethacin | (2:1) and (5:1) |
| vi) | Flufenamic acid | (2:1) and (5:1) |
| vii) | Ibuprofen | (5:1) |

CARDIOVASCULAR AGENTS

| | |
|---|---|
| i) Atenolol | (5:1) |
| ii) Diltiazem HCl | (2:1) and (5:1) |
| iii) Diltiazem Base | (5:1) |

Propranolol HCl and propranolol base both dissolved slowly to form a hazy solution which did not precipitate out. Nifedapine and verapamil formulations did not show any apparent tendency to dissolve.

b) Solubility in Water

The following dissolved in water to form a clear stable solution at 25°C and 37°C.

| | |
|---|---|
| i) Ibuprofen | (5:1) |
| ii) Atenolol | (5:1) |
| iii) Diltiazem HCl | (2:1) and (5:1) |
| iv) Diltiazem Base | (5:1) |

c) Solubility at pH 1.27

None of the formulations illustrated in the examples formed a clear stable solution at pH 1.27. However, the following produced a clear solution over a gummy solid:

| | |
|---|---|
| i) Diltiazem HCl | (2:1) and (5:1) |
| ii) Propranolol HCl | (5:1) |
| iii) Verapamil | (2:1) and (5:1) |
| iv) Diclofenac | (2:1) and (5:1) |
| v) Sulindac | (2:1) and (5:1) |

Example 49 - Pharmacological Study

Experiments described in this example were designed to investigate the effects of a mixture of bile acids on the absorption of propranolol from the gastrointestinal tract via the hepatic portal blood supply and the lymphatic system. Standard surgical procedures were used to enable samples of lymph, portal and systemic blood to be collected under anaesthesia. Formulations under test were administered in a solution dissolved in 20ml of pH 7.4 gastrointestinal buffer, via a gastrointestinal catheter. The formulations were as follows.

**Formulation A** - Ox bile extract and propranolol base, in the ratio 5:1 by weight as prepared in Example 16. The total dose was 12mg/kg body weight (equivalent dose of propranolol 2mg/kg).

**Formulation B** - Ox bile extract and propranolol hydrochloride, in the ratio 5:1 by weight as prepared in Example 15. The total dose was 12mg/kg body weight (equivalent dose of propranolol 2mg/kg).

**Formulation C** - Propranolol hydrochloride, 2mg/kg.

Lymph and blood samples were taken 5 minutes after administration of the test solution and then at 15 minute intervals for 240 minutes. All samples were collected in heparin to prevent coagulation. Blood samples were centrifuged to remove red blood cells and stored at $4^{o}C$. Plasma samples were extracted by passing plasma through VAC-ELUTE mini-$C_{18}$ columns. Propranolol

was eluted from the columns with a mixture of acetonitrile and 0.1M hydrochloric acid (1:1 v/v), analysed by high pressure liquid chromatography and quantified by comparison with authentic standards using fluorescence detection.

The study was carried out using 4 pigs - A, B, C and D. The formulation each pig received was as follows:

Pig A - Formulation A
Pig B - Formulation B
Pig C - Formulation C
Pig D - Formulation B

Pig D, in addition to Pig B, received formulation B because of hepatic portal vein and lymphatic catheter failure in Pig B. In this animal, the portal vein cannula was defective throughout the study, whereas the lymphatic cannula became obstructed about 45 minutes after administration of the test solution.

The lymph flow for each pig was recorded before and after administration of the test solutions. In addition, the levels of propranolol found in the lymph samples collected were measured. In order to ascertain the overall effects of compositions in accordance with the invention on lymphatic drug delivery, the cumulative amount of propranolol secretion in the lymph was derived from the lymph flow and the rate of lymphatic secretion of propranolol. Table 1 below shows the total amount of propranolol secreted into the lymph after the time indicated.

TABLE 1

| Pig | Amount of Propranol Secretion | Time |
|---|---|---|
| A | 675 ng | 240 minutes |
| B | 1030 ng | 60 minutes |
| C | 300 ng | 240 minutes |
| D | 1025 ng | 240 minutes |

These results indicate that the formulations containing the bile salt mixtures are capable of increasing the total dose of propranol absorbed through the lymph by a factor of at least 2, and perhaps as much as 10 (if the rate of secretion in Pig B were to be extrapolated to 240 minutes). These results are illustrated in Figure 1.

The cumulative absorption of propranolol via the hepatic portal blood supply was also measured, and the results are shown in Figure 2. It should be noted that levels of propranolol are in relative units, as, under the protocol used, no measure of portal blood flow could be made.

It can be seen that the bile acid mixture generally delays the absorption of propranolol via the hepatic portal route, and in the case of Formulation B, they signficantly reduce the extent of absorption via this pathway.

EXAMPLE 50

This example concerns the combination of bile acids, propranolol HCl and the monoglyceride glycerol mono-oleate.

| | |
|---|---|
| Ox Bile Extract | 78% |
| Propranolol HCl | 14% |
| Glycerol mono-oleate | 8% |

The components were dissolved in excess (80%) alcoholic solvent and then recrystallized as a green solid. This material was packed into hard gelatin capsules which were then enterically coated using hydroxypropyl methylcellulose phthalate (HP55 by Shin-Etsu) in an ethanol/water solvent system.

The composition of the enteric coating solution was:

| | |
|---|---|
| HP55 | 6% |
| Ethanol | 84.5% |
| Purified water | 9.5% |

The solution was applied to capsules, previously sealed using a LICAPS Test Kit supplied by CAPSUGEL, in a UNI-GLATT fluidized bed. (The words LICAPS, CAPSUGEL and UNI-GLATT are trade marks.) The resulting batch (D180) was subject to testing in human subjects.

EXAMPLE 51

This example concerns the use of the unsaturated fatty acid oleic acid together with ox bile extract and propranolol HCl.

| | |
|---|---|
| Ox bile extract | 67% |
| Propranolol HCl | 13% |
| Oleic acid | 20% |

The components were mixed with and recrystallized from excess (800%) alcoholic solution. The resulting green crystalline solid was packed into hard gelatin capsules and sealed using a LICAPS Test Kit supplied by CAPSUGEL. The capsules were subsequently enteric coated using hydroxypropyl methylcellulose phthalate (HP55).

The enteric coating solution contained:

| | |
|---|---|
| HP55 | 6% |
| Ethanol | 84.5% |
| Purified water | 9.5% |

and was applied using a UNI-GLATT fluidized bed system. The resulting batch (D179) was used in a human bioavailability study.

EXAMPLE 52 - Pharmacological Study

Study Design

This clinical trial was a three way cross-over study using nine subjects. The dose used in each case was 80mg of propranolol in the form of two separate formulations in accordance with the invention: D179, produced in Example 51 (Treatment A) and D180, produced in Example 50 (Treatment B); or Inderal (ICI) (Treatment C). Subjects were fitted with a venous catheter and an initial blood sample taken. Further blood samples were taken at 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h and 24h.

A brief medical record of the patients was taken, together with an examination to ensure they were in good health. History of smoking habits, alcohol and caffeine consumption were recorded, together with age, weight and height.

Blood samples were collected into EDTA Vacutainers (trade mark) and plasma retained after centrifugation for 15 minutes at 2500 rpm to remove red blood cells. Plasma samples were immediately frozen and then stored at -20°C until analysed using the HPLC method described previously.

Results and Discussion

The plasma levels of propranolol determined in each sample collected from the subjects during each treatment were recorded against time. A comparison of

the area under the curve (AUC) achieved with each treatment is listed in Table 1. The mean increase in AUC of Treatment B over control was 35% while the mean increase using Treatment A was 20%. A further comparison between treatments was made on the basis of peak plasma concentrations (See Table 2). The mean increase in peak plasma propranolol levels was 56% using Treatment B and 37% using Treatment A compared to control Treatment C.

TABLE 1

A.U.C. (ng.h/ml)

| | D180 | D179 | Inderal | | | |
|---|---|---|---|---|---|---|
| Subject | A | B | C | A/C | B/C | B/A |
| I | 409 | 635 | 388 | 1.05 | 1.64 | 1.55 |
| II | 634 | 810 | 608 | 1.04 | 1.33 | 1.28 |
| III | 1143 | 1020 | 470 | 2.43 | 2.17 | 0.89 |
| IV | 551 | 902 | 698 | 0.79 | 1.29 | 1.64 |
| V | 375* | 670 | 387 | 0.97 | 1.73 | 1.79 |
| VI | 399* | 136 | 354 | 1.13 | 0.38 | 0.34 |
| VII | 242 | 355 | 272 | 0.89 | 1.31 | 1.47 |
| VIII | 1684 | 1321 | 1472 | 1.14 | 0.90 | 0.78 |
| IX | 368* | 358* | 264 | 1.39 | 1.36 | 0.97 |
| Mean | 645 | 690 | 546 | 1.20 | 1.35 | 1.19 |
| s.d. | 470 | 371 | 376 | 0.49 | 0.51 | 0.48 |
| CV(%) | 73 | 54 | 69 | 41 | 38 | 40 |

TABLE 2

Peak (ng/ml)

| | D180 | D179 | Inderal | | | |
|---|---|---|---|---|---|---|
| Subject | A | B | C | A/C | B/C | B/A |
| I | 62 | 86 | 46 | 1.35 | 1.87 | 1.39 |
| II | 93 | 138 | 67 | 1.39 | 2.06 | 1.48 |
| III | 178 | 134 | 57 | 3.12 | 2.35 | 0.75 |
| IV | 98 | 105 | 213 | 0.46 | 0.49 | 1.07 |
| V | 35 | 84 | 47 | 0.74 | 1.79 | 2.40 |
| VI | 58 | 58 | 56 | 1.04 | 1.04 | 1.00 |
| VII | 35 | 70 | 38 | 0.92 | 1.84 | 2.00 |
| VIII | 218 | 203 | 247 | 0.88 | 0.82 | 0.93 |
| IX | 69 | 50 | 28 | 2.46 | 1.79 | 0.72 |
| | | | | | | |
| Mean | 94 | 103 | 89 | 1.37 | 1.56 | 1.30 |
| s.d. | 64 | 48 | 81 | 0.87 | 0.62 | 0.58 |
| CV(%) | 68 | 47 | 91 | 63 | 40 | 44 |

CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically active agent, a bile salt and at least one additional component (other than water) of bile.

2. A composition as claimed in claim 1, wherein the additional component is a different bile salt and/or a biliary lipid.

3. A composition as claimed in claim 1, wherein the bile salt and additional component are provided in a naturally occurring mix of bile components.

4. A composition as claimed in claim 3, wherein the naturally occurring mix of bile components comprises animal bile or an extract of animal bile.

5. A composition as claimed in claim 4, wherein the extract of bile is obtained by evaporating natural bile to dryness.

6. A composition as claimed in claim 4, wherein the extract of bile is prepared by extraction with an organic solvent.

7. A composition as claimed in claim 6, wherein the organic solvent is methanol.

8. A composition as claimed in claim 1, which is substantially non-aqueous.

9. A composition as claimed in claim 1, comprising a lymphatic absorbtion promoter.

10. A composition as claimed in claim 9, wherein the lymphatic absorbtion promoter is oleic acid and/or glycerol mono-oleate.

11. A composition as claimed in claim 1, wherein the pharmaceutically active agent is a non-streoidal anti-inflammatory drug.

12. A composition as claimed in claim 1, wherein the pharmaceutically active agent is normally subject to significant hepatic first-pass metabolism.

13. A composition as claimed in claim 1, wherein the pharmaceutically active agent is a cardiovascular agent.

14. A composition as claimed in claim 14, wherein the cardiovascular agent is propranalol, metoprolol, verapamil, nifedipine, diltiazem, atenolol and/or nadolol.

15. A process for the preparation of a pharmaceutical composition, the process comprising admixing a pharmaceutically active agent, a bile salt and at least one additional component (other than water) of bile.

1/2

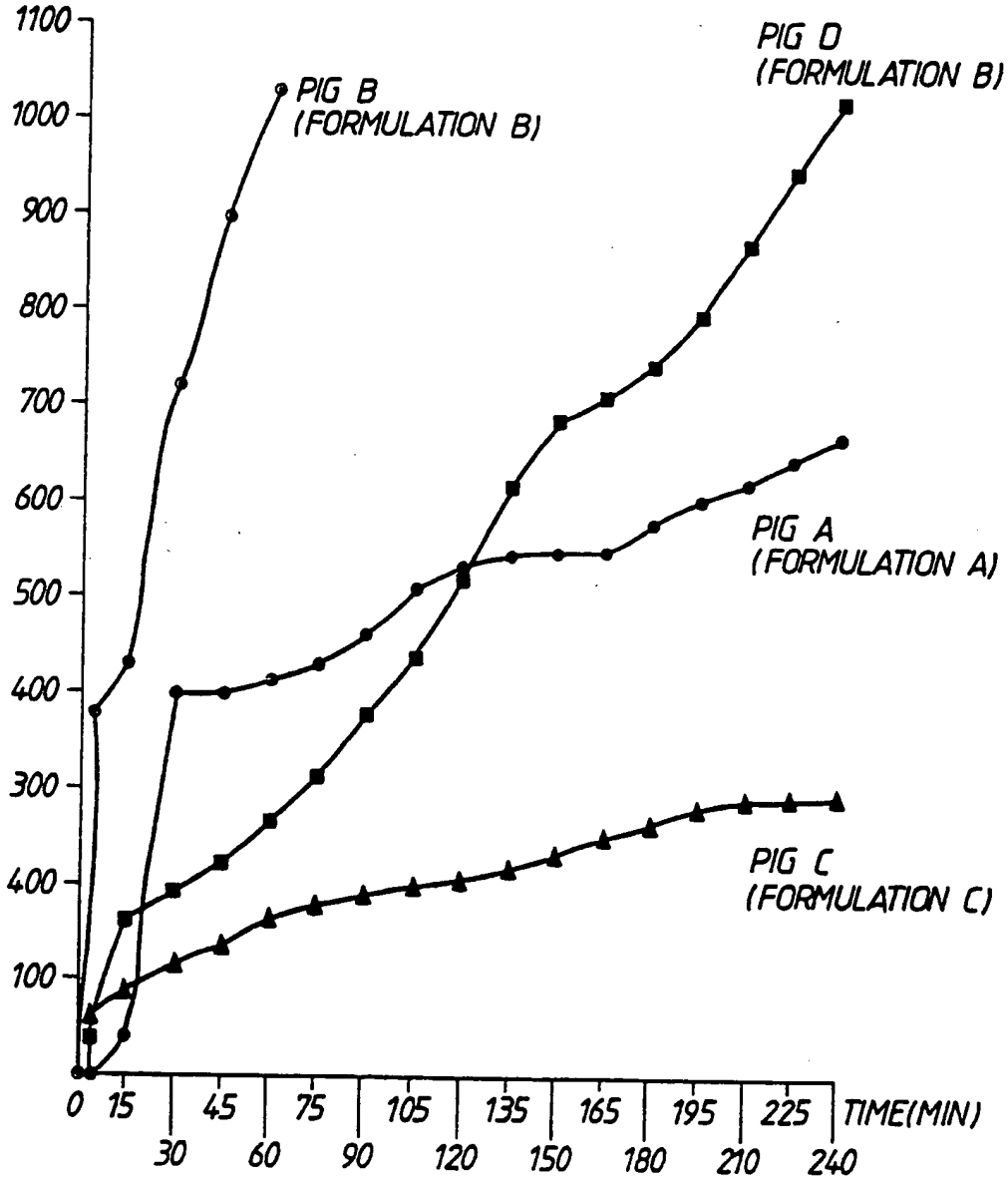
1100
1000
900
800
700
600
500
400
300
400
100
PIG B
(FORMULATION B)
PIG D
(FORMULATION B)
PIG A
(FORMULATION A)
PIG C
(FORMULATION C)
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 240
TIME(MIN)

Fig.1.

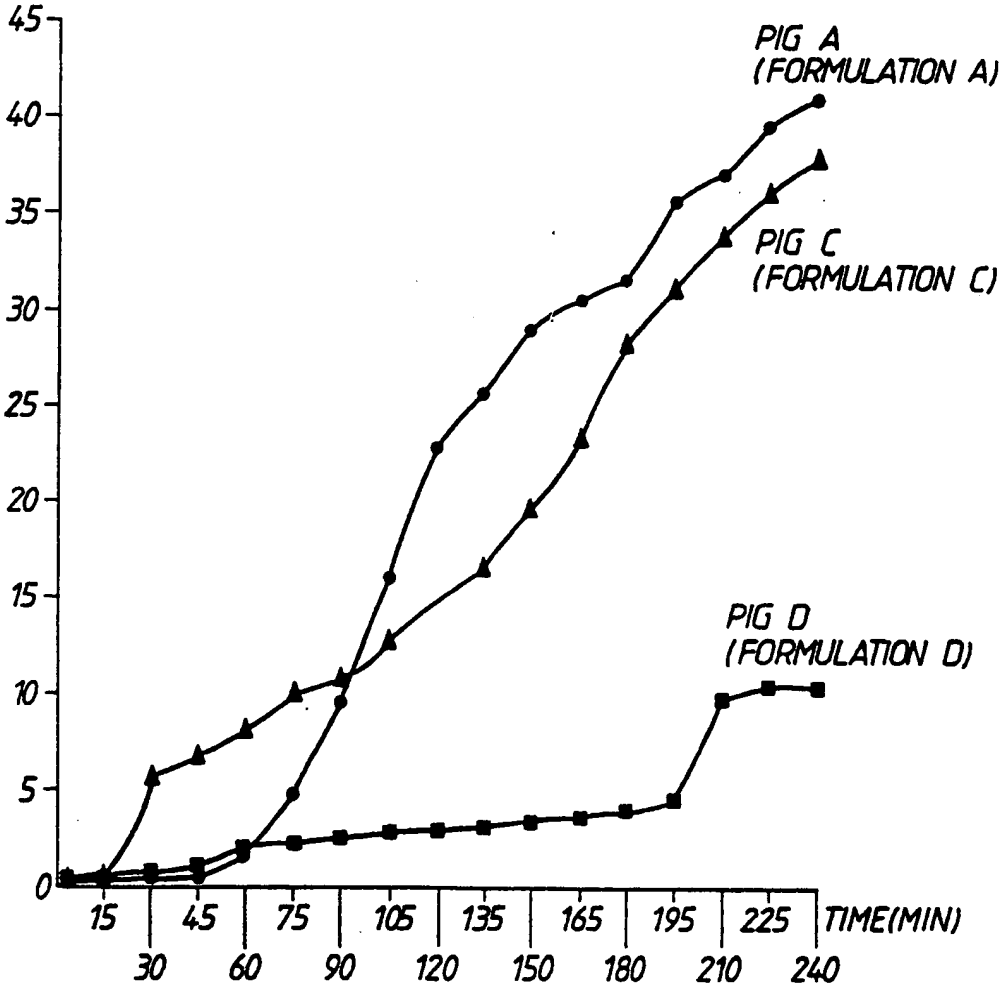
45
40
35
30
25
20
15
10
5
0
PIG A
(FORMULATION A)
PIG C
(FORMULATION C)
PIG D
(FORMULATION D)
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
TIME(MIN)

Fig.2.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/00605

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 35/413, 45/06, 47/12, //(A 61 K 35/413, 33:575, 31:405, 31:19, 31:135)

## II. FIELDS SEARCHED

Minimum Documentation Searched [7]

| Classification System | Classification Symbols |
|---|---|
| IPC[5] | A 61 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

| Category [10] | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| X | Unlisted Drugs, volume 23, no. 3, March 1971 (Chatham, New Jersey, US), see page 41, K "QUINZYME" | 1-8 |
| X | Unlisted Drugs, volume 26, no. 1, January 1974, (Chatham, New Jersey, US), see page 12, J "ZYMAZA" | 1-8 |
| X | Unlisted Drugs, volume 26, no. 7, July 1974, (Chatham, New Jersey, US), see page 115, L "STO-ZYME" | 1-8 |
| A | FR, A, 2427100 (KALI-CHEMIE PHARMA GmbH) 28 December 1979 see page 10, line 1 - page 12, line 20; claims 1-24 | 1-15 |

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 25th July 1990 | 14.08.90 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | R.J. Eernisse |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, 11 with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| A | Chemical Abstracts, volume 102, no. 17, 29 April 1985, (Columbus, Ohio, US), M.R. Gasco et al.: "The influence of bile salts on the absorption in vitro and in vivo of propanolol", see page 12, abstract 142751u, & J. Pharm. Biomed. Anal. 1984, 2(3-4), 425-39 (Eng). see the abstract | 1-15 |
| A | EP, A, 0179583 (MERCK & CO. INC.) 30 April 1986 see page 13, lines 15-18; example 4 cited in the application | 1-15 |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9000605 SA 36346

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 10/08/90
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| FR-A- 2427100 | 28-12-79 | NL-A- 7806048 | 04-12-79 |
| EP-A- 0179583 | 30-04-86 | AU-A- 4825285 | 10-04-86 |
| | | JP-A- 61091117 | 09-05-86 |